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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/585,645 | 06/01/2000 | Huda Y. Zoghbi | P01899US2 | 4965 |

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EXAMINER

QIAN, CELINE X

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1636

DATE MAILED: 11/19/2002

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/585,645

Applicant(s)

ZOGHBI ET AL.

Examiner

Celine X Qian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 September 2002.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 40-48, 50, 112-119, 121 and 123 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 40-48, 50, 112-119, 121 and 123 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Claims 40-48, 50, 112-119, 121 and 123 are pending in the application.

This Office Action is in response to the Amendment filed on 9/13/02.

Response to Amendment

The objection to claims 40-48, 50, 112-119, 121 and 123 has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 40-48, 50 and 116 under 35 U.S.C. 112 second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The objection to the specification is maintained for reasons discussed below.

The rejection of claims 40-48, 50, 112-119, 121 and 123 under 35 U.S.C. 112 first paragraph (written description) is maintained for reasons set forth of record mailed on 6/3/02 and further discussed below.

The rejection of claims 40-48, 50, 112-119, 121 and 123 under 35 U.S.C. 112 first paragraph (enablement) is maintained for reasons set forth of record mailed on 6/3/02 and further discussed below.

The rejection of claims 114 and 117 under 35 U.S.C. 112 second paragraph is maintained for reasons set forth of record mailed on 6/3/02 and further discussed below.

Specification

Applicants failed to correct the informality that is objected to in the previous Office Action: The amino acid sequence on page 33 line 22 lacks sequence identifier. The specification remains objected to. Any response to this office action which does not response to the above objections will be considered non-responsive.

Claim Objections

Claim 48 and 113 are objected for containing non-elected subject matter. (see previous office action). Any response to this office action which does not response to the above objections will be considered non-responsive.

Response to Arguments

Issues under 35 U.S.C. § 112, second paragraph

In response to the rejection of claim 114, Applicants argue that the specification defines vector as “a biological vehicle for delivery of a specific entity,” so that the terms “liposome, protein, lipid and carbohydrate” are well within the scope of the definition.

This argument has been considered but deemed not persuasive. Although Applicants may be their own lexicographers, the “vector” as recited in claim 114 must be put into context. Claim 114 depends on 113 which clearly recites “a vector that expresses an atonal-associated nucleic acid sequence in an animal cell.” Such a vector is not only a biological vehicle for delivery of a specific entity, but also must be able to express a nucleic acid sequence. It is unclear how a “liposome, protein, lipid or carbohydrate” can express a nucleic acid sequence. Therefore, the claim is indefinite.

In response to the rejection of claim 117 in regarding to the term “protein transduction domain,” Applicants argue that the meaning of the term is well known. Applicants further argue that the specification (page 72, lines 2-6, and Example 22) provides a well-known example of said term, the HIV Tat protein. However, HIV Tat is well known as comprising a “protein translocation domain.” The specification does not otherwise define “protein transduction domain” besides the example provided. If HIV Tat represents the full scope of this term, then

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the claim is definite. Otherwise, the meaning of “protein transduction domain” is still unclear since it is not recognized in the relevant art. As such, claim 117 is indefinite.

Issues under 35 U.S.C. §112, first paragraph (written description)

In response to the claims 40-48, 50, 112-119, 121 and 123, Applicants argue that the claimed invention is written and describes a sufficient amount of embodiments to show possession. Applicants indicate that a plethora of exemplary atonal-associated sequences derived from a variety of animal species are provided (page 28-29), and conclude that given the many disclosed examples, a skilled artisan would be well taught which atonal-associated sequences would be useful and would perceive that the Applicants as having possession of the invention. Applicants further argue that the function of the multitude of atonal sequences is irrelevant. Applicants further assert that the claims are not limited to a particular domain for the atonal-associated nucleic acid sequence, and as long as Applicants have described the invention, directed to utilizing an atonal-associated sequence, the requirement of written description is met. Applicants' arguments have been fully considered but deem not persuasive. In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. The claims as amended clearly encompass atonal-associated nucleic acid sequences encodes a polypeptide that has hair generating activity and has at least about 80% identity to about 20 contiguous residues of any region of SEQ ID NO: 58. The claimed polypeptide (in theory) ranges from 20 amino acid residues to infinite length as long as it comprises 20 amino acid that is 80% homologous to any region of SEQ ID NO: 58. The claimed polypeptide may be structurally completely different

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protein than the polypeptide encoded by SEQ ID NO: 58. The examples provided by the specification (on page 28-29) represent only a fraction of the species in the genus as claimed.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Contrary to Applicants' assertion, the function of the atonal associated sequence is relevant because it is the identifying characteristics shared by these sequences as claimed. The claim recites that the polypeptide has hair generating activity. However, the specification does not describe any other polypeptides having hair generating property other than Math1. According to MPEP 2163, a biomolecule sequence described only by a functional characteristic (i.e. hair generating activity), without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes... The Federal Circuit has pointed out that under United States law, a description that does not render a claimed invention obvious cannot sufficiently describe the invention for the purposes of the written description requirement of 35 U.S.C. 112. *Eli Lilly*, 119 F.3d at 1567, 43 USPQ2d at 1405. Compare *Fonar Corp. v. General Electric Co.*, 107 F.3d 1543, 1549, 41 USPQ2d 1801, 1805 (Fed. Cir. 1997) (See MPEP 2163). Therefore, the structural function relationship of the atonal-associated sequences is relevant and important to satisfy the written description requirement. However, such relationship is not clearly described in the instant specification because it is unclear which 20 contiguous residues of SEQ ID NO:58 is necessary for the function of the polypeptide they encode. As such, the specification fails to describe the invention in such a way to convey one skilled in the art that the inventors have possession of the invention at the time of filing.

Issues under 35 U.S.C. §112, first paragraph (enablement)

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In response to the rejection of claims 40-48, 50, 112-119, 121 and 123, Applicants argue that the specification supports the enablement of the claims because the specification comprehensively describes delivery of nucleic acid sequences both generally and in exemplary embodiments (page 55-58, and examples 14-21). Applicants further provide references that teach administration of Math 1 results in extra hair cells in postnatal rate cochlear explant cultures (Zheng and Gao) and methods for inner ear gene transfer (Kawamoto et al. and Kanzaki et al.) and conclude that such teaching provides additional support for generating hair cells in inner ear by delivering atonal-associated nucleic acid sequences to an animal. Applicants further provide case laws that support the arguments that the instant specification met the burden for enablement under 35 U.S.C. 112, first paragraph. Applicants assert that the disclosure complies with the requirement of M.P.E.P.2164.03. Furthermore, Applicants point out that the claims may encompass inoperative embodiments (such as where a particular atonal associated nucleic acid sequence is not effective for the generation of hair cells) as supported by case law *Atlas Powder Co. v. E. I. DuPont de Nemours & Co.* Finally, Applicants argue that the mechanism or the function of the polypeptide domain by which atonal is effective for hair cell generation is irrelevant to the patentability of the claims, and one skill in the art would not require undue experimentation to practice said invention.

The above arguments and references cited have been fully considered and deemed partially persuasive. Based on the disclosure of the instant specification and the teaching from art at the time of filing, the specification is enabled for a method of generating inner ear hair cells in an animal by direct injection of a nucleic acid encoding Math 1 to inner ear cells. However, the specifications fails to provide sufficient support for a method of generating hair cells

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anywhere else on the body of the animal by administering any atonal associated sequence that has hair generating activity and at least 80% homology with SEQ ID NO:58. The specification also fails to provide support for generating inner ear cells by administering Math 1 via other methods.

The reasons for the non-enablement rejection were discussed in detail in the Office Action set forth of the record mailed on 6/3/02. The following discussion is in response to Applicants' arguments as summarized above.

M.P.E.P 2164.03 states that "it is well settled that ...that the chemical or chemical combination included in the claims are capable of accomplishing the desired result." (as quoted by Applicants on page 9, Amendment D) This means that any atonal associated sequence that has hair generating activity and at least 80% homology with SEQ ID NO:58 must be able to generating hair cells in any region of the body. However, as discussed in the previous office action, the specification fails to disclose any atonal associated sequences other than Math 1 have hair generating property. The art does not teach whether other atonal associated sequences having 80% homology with any 20 contiguous amino acid residue is able to generate hair cells. In addition, neither the specification nor the prior art teach whether Math 1 can generate hair cells elsewhere in the body. As discussed in the previous office action, the genes involves in different types of hair cell development and differentiation are not the same. Therefore, whether Math 1 can generate hair cells in any part of the body is unpredictable. In addition, whether any other atonal associated sequence can generate hair cells in any part of the body is also unpredictable.

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Although *Atlas Powder Co. v. E. I. DuPont de Nemours & Co.* decides in that case the claims may encompass inoperative embodiments which does not necessarily render them non-enabled, the case law further states that if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). In the instant case, the number of inoperative embodiments is significant in regard of the unpredictability of both using any atonal associated sequence having 80% homology with 20 contiguous sequence as SEQ ID NO: 58 and generating hair cells on any part of the body. In addition, besides direct injection of the nucleic acid to the inner ear, neither the specification nor the art provide enough support for delivering effective amount of atonal associated sequence to inner ear that would overcome the technical difficulties as discussed in the previous office action. Therefore, considering the breath of the scope and limited teaching from the specification, one skilled in the art would have to engage in undue amount of experimentation to practice the invention in commensurate with the scope the invention. The invention as claimed is only enabled for a method of generating inner ear hair cells in an animal by direct injection of a nucleic acid encoding Math 1 to inner ear cells.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO**

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
November 15, 2002



JAMES KETTER
PRIMARY EXAMINER